Editorials

Seminars in Health Care Delivery

AT A RECENT Annual Meeting of the Editorial Board it was suggested that in view of the growing importance of socioeconomics in the delivery of health care, the journal should begin to offer more on this subject for the information and perusal of its more than 54,000 readers. In response to this suggestion a series of Seminars in Health Care Delivery was planned.

The editors were fortunate indeed when Steven A. Schroeder, MD, agreed to be the editor for this series. Dr Schroeder not only is a distinguished clinician, a leading teacher of primary care internal medicine and consultant to a number of private foundations and government agencies, but he also is widely known for his scholarship and publications in many aspects of health care delivery. Among his many responsibilities, he currently serves as a member of the US Prospective Payment Assessment Commission and chairman of its Data Development Committee.

The journal welcomes Dr Schroeder and looks forward to the series of Seminars in Health Care Delivery that is being developed under his leadership, the first of which appears in this issue.

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New Roles for Activated Charcoal

DERLET AND ALBERTSON in their excellent review entitled "Activated Charcoal—Past, Present and Future" in this edition of the journal have provided a scholarly summary of the development, current uses and new roles of oral activated charcoal in the treatment of poisoned patients. They not only focus on the use of activated charcoal as an adsorbent of many common poisons and drugs to prevent their absorption from the gut but also review the role of multiple doses of oral charcoal in increasing the clearance of certain substances from the body (gastrointestinal dialysis).

As pointed out by the authors, a new form of superactivated charcoal is available and has been recently released for clinical use in the United States.[1] This charcoal (Super-Char) has a surface area of 2,500 to 3,500 m^2 per gram, or approximately three times as much as the older forms of activated charcoal.[1] This substance, as expected, is approximately three times as effective (on a weight basis) in both adsorbing drugs and in increasing the clearance of drugs from the body. The advantage of superactivated charcoal is that only approximately a third the amount of standard charcoal is necessary to decrease absorption or increase clearance of intoxicants comparably. There are some patients who are unable to drink 60 grams of charcoal but who can drink 20 grams. Thus, superactivated charcoal is an important advance in charcoal preparations and its use has been adopted in many institutions in the United States.

Activated charcoal use is not without limitations. Many drugs and intoxicants are not well adsorbed by activated charcoal, as pointed out by Derlet and Albertson. These include lithium, methanol and ethylene glycol. Moreover, there are other drugs that, although they are adsorbed by activated charcoal, their clearance is not accelerated by multiple doses of oral charcoal.[1] For example, in one carefully done study with intravenously given imipramine hydrochloride (a tricyclic antidepressant), the imipramine clearance in subjects receiving multiple doses of activated charcoal was no greater than in those who received no charcoal.[2] Similarly, digoxin clearance is only increased by approximately 30% with multiple doses of oral activated charcoal in normal subjects.[1] It is experimentally clear, however, that many drugs, including salicylates, barbiturates, carbamazepine, dapsone, digitoxin, nadolol, theophylline and the pesticide chlordecone, have greatly increased clearances by multiple doses of oral activated charcoal.[1]

In previous publications, we have proposed a simple pharmacokinetic model to explain the ability or lack of ability of multiple doses of activated charcoal to increase the clearance of drugs and poisons from the body.[1,3] The total body clearance (Cl_T) of a drug or poison is the summation of clearances by all methods of removal from the body. Thus,

$$Cl_T = Cl_K + Cl_L + Cl_{GI},$$

where the subscripts K, L and GI refer to elimination by the kidney, metabolism and excretion by the liver and removal by charcoal through the gastrointestinal tract, respectively. Therefore, the significance of the contribution of charcoal on Cl_{GI} to Cl_T will depend on the magnitudes of Cl_{GI} relative to Cl_K and Cl_L. We have shown this by comparing the effect of charcoal on the clearance of theophylline as a model drug in normal subjects and patients with hepatic cirrhosis. As the endogenous theophylline clearance (Cl_L and Cl_K, due to hepatic and renal elimination) decreased in normal subjects and in patients with hepatic dysfunction, the effect of charcoal (Cl_{GI}) on theophylline clearance (Cl_T) increased.[1,3] Therefore, even if endogenous clearance declines to zero, the total clearance (Cl_T) will never be less than the Cl_{GI} achieved by charcoal in the gut.

The rate of removal of a drug or poison by charcoal in the gut is strongly influenced by the apparent volume of distribution (V) of the drug or poison.[1]

$$\text{Rate of removal by charcoal} = Cl_{GI} \times C$$
$$= Cl_{GI} \times A/V,$$

where C is the concentration of drug or poison in the plasma and A is the amount of drug or poison in the body. Therefore, for any given amount of drug or poison (A) and clearance rate (Cl_{GI}), the rate of removal by charcoal in the gut is inversely related to the volume of distribution. That is, drugs with large volumes of distribution will not be effectively removed by oral activated charcoal. An example of such a drug is imipramine.

We can make some general predictions as to which drugs and poisons may or may not be effectively removed from the body by multiple doses of oral activated charcoal.[1] It would be expected that drugs or poisons that can easily diffuse across the gut membrane and have small volumes of distribution (less than 1 liter per kilogram of body weight) would be effectively

removed. Theophylline, phenobarbital and digitoxin generally fit these criteria. Conversely, digoxin and tricyclic antidepressants such as imipramine have large volumes of distribution and show limited removal by charcoal. Overall, the principles that govern the ability of oral activated charcoal to increase the clearance of drugs and poisons from the body are analogous to the principles that govern the effectiveness of hemodialysis and hemoperfusion for removing drugs and poisons. Major exceptions to this generalization are drugs and poisons that are not adsorbed by charcoal or that do not enter the gut from the blood. For example, we would not expect aminoglycoside antibiotics to be effectively removed since they do not cross the gut membrane, as evidenced by lack of absorption when they are administered orally.

Of course, this model for increasing drug clearance with activated charcoal assumes that adequate charcoal is given to fill the gut lumen.[1] This is done generally by giving doses of approximately 20 grams of superactivated charcoal every two hours for maximum effect.[1] Activated charcoal can also be used as an adsorbent in hemoperfusion systems to increase the clearance of drugs, but this is beyond the scope of this editorial.[4]

In summary, there is no question that charcoal given orally, especially superactivated charcoal, can decrease the absorbance of many drugs from the gut and, in many cases, increase the clearance of drugs from the body, sometimes substantially. Thus, there is no doubt about the pharmacokinetic efficacy of charcoal as both an adsorbent and a substance to increase clearance. What has never been clearly established, however, is that these impressive pharmacokinetic properties of charcoal are, in fact, related to better patient outcome.[5] Derlet and Albertson in their review discuss this important point and we would reemphasize this question. First principles in pharmacology and medicine would strongly suggest, that, if less drug or intoxicant is absorbed, the patient will have less of a toxic reaction; or, if the drug or intoxicant is more rapidly removed, the patient will suffer less adverse effects. This should result in less morbidity—that is, shorter times in intensive care units. These assumptions, however, remain to be established conclusively in controlled clinical trials.

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Need Kidneys Fail?

THE RATE OF PROGRESSION to end-stage renal failure is not influenced solely by the extent and severity of the primary renal insult. Amplifiers of risk include systemic hypertension, urinary tract infection or obstruction and intrarenal deposition of calcium and urate salts. Often, however, despite control of these risk factors, mild but permanent kidney injury eventually results in progressive deterioration of renal function. These observations suggest that reduction of the number of functioning nephrons beyond a certain point ultimately leads to failure of the remaining nephron units. Investigation into the mechanism(s) responsible for this process in animals has shown that progressive loss of these residual nephrons is a predictable consequence of the glomerular hemodynamic response to renal injury and, in particular, to the adaptive increase in glomerular capillary hydraulic pressure that regularly follows a decline in the number of functioning nephrons.[1] Some of the evidence upon which our hypothesis is built is reviewed by Avasthi elsewhere in this issue.

A pattern of progressive azotemia, proteinuria and glomerular sclerosis similar to that found in animals after partial renal ablation is also observed in clinical settings following a circumscribed renal injury. These include bilateral renal cortical necrosis and vesicoureteral reflux. Likewise, acute poststreptococcal glomerulonephritis and the various forms of lupus nephritis occasionally progress to chronic renal failure in the absence of continued immunologic injury. Hemodynamic factors may also explain the observation that pregnancy, with its attendant increments in glomerular filtration rate and renal blood flow, frequently accelerates a loss of renal function in women with preexisting kidney disease.

These observations therefore urge the answering of a number of clinical questions. First, what degree of renal mass reduction in humans results in progressive glomerular disease? Some information in this regard is available from studying cases of the congenital renal disease, oligomeganephronia, a condition characterized by a reduction in nephron number to approximately 20% of the normal complement and by pronounced hypertrophy of those nephrons present. Hyperfiltration per nephron in this disorder initially maintains the total glomerular filtration rate at an acceptable level, but by adolescence children with this condition typically have progressive proteinuria, glomerular sclerosis and renal failure. More common is unilateral renal agenesis, where glomerular hyperfiltration in a solitary kidney maintains renal function at near-normal levels during childhood, only to eventuate in the development of renal failure in early adult life in some affected persons. It would thus appear that a reduction of renal mass by half or more during very early life imposes a risk, as yet unquantified, for subsequent hemodynamically mediated overt renal injury.

A second important question is whether increased glomerular capillary pressures can initiate progressive glomerular disease even when the number of functioning nephrons is normal. We have suggested that the protein-rich diet characteristic of modern Western society may induce chronic renal hyperperfusion and hyperfiltration, thereby contributing to the glomerulosclerosis seen with aging.[1] The recent observation that clinically overt proteinuria and renal insufficiency are more likely to develop in those patients with type I diabetes who have substantial hyperfiltration early in the course of their disease than in those patients with lesser initial degrees of hyperfiltration also supports an affirmative answer to this question.[2] Additional support is found in sickle cell anemia, which, although classically associated with papillary